

Fast Dissolving Oral Films: A Review

Shivangi Singh, Swati Dixit, Dr Alka Verma, Dr Mohammad Faizan and Neha Jaiswal

Rameshwaram Institute of Technology and Management, Lucknow, Uttar Pradesh, India

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Abstract— Oral fast dissolving film (OFDF) is a new method that enhances consumer acceptability due to its quick disintegration and the ability to be self-administered without the need for water or chewing. The movie serves as an optimal method for delivering drugs that dissolve rapidly inside the mouth. Various medications, such as neuroleptics, cardiovascular pharmaceuticals, analgesics, antihistamines, antiasthmatic drugs, and treatments for erectile dysfunction, may be produced as mouth dissolving films. Several procedures were available for preparing oral films in the buccal cavity. The buccal cavity is a component of the mouth that has a mucosal layer which efficiently absorbs and distributes substances throughout the body. This review provides an overview of the many techniques used for preparing oral films, including the selection of suitable polymers for formulation. It also discusses the several technologies involved in the process, as well as the assessment criteria used to assess the quality of the films. Finally, the article explores the various uses of oral films.

Keywords— Oral fast dissolving film (OFDF), drug delivery, buccal cavity, polymer formulation, quality assessment.

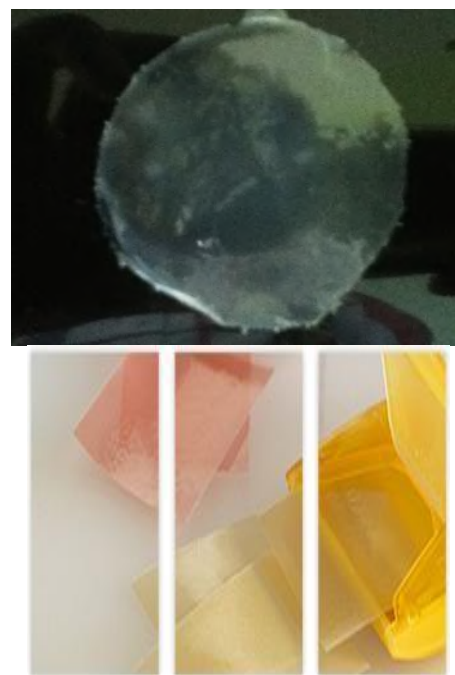


I. INTRODUCTION

The oral route remains the most favoured method for drug delivery due to its numerous advantages over other administration routes. However, there is still room for improvement in oral drug delivery systems, particularly for certain patient groups such as the elderly, children, and individuals with dysphagia or other medical conditions that make it challenging to swallow or chew solid dosage forms. Despite the rapid dissolution of tablets, there is a concern about the risk of choking owing to their tablet-like form. One of the most important elements that affects how well children follow their prescribed medication regimes is how easy it is for them to swallow the medicine.

While solid dose forms are generally well-received by older individuals and teenagers, smaller children often have a preference for liquid formulations due to their ease of swallowing [3]. Various innovative approaches for administering medications orally have recently emerged to specifically target the physicochemical and pharmacokinetic properties of the pharmaceuticals, with the aim of enhancing patient adherence. Additionally, there have been significant advancements in electrostatic drug deposition and coating [4,6], as well as computer-assisted three-dimensional

printing (3DP) for tablet manufacturing [5,6].

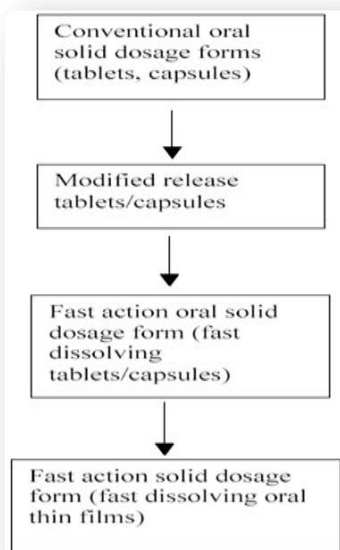


Examples of Film

So, Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Advancements in oral drug administration have resulted in the evolution of dosage forms from traditional tablets or capsules to modified release tablets or capsules, and further to oral disintegrating tablets (ODTs), wafers, and the more recent invention of oral fast dissolving films (OFDFs). Among the many options being investigated for the development of fast-acting drug delivery systems, oral strip technology is receiving significant interest [6,7]. The development and widespread usage of Listerine pocket strips in the early 2000s made (ODFT) popular among the public.

According to Technology Catalysts, the market value of medicinal products in oral thin film formulations was estimated to be \$500 million in 2007 and is projected to potentially reach \$2 billion in the near future [7,8,18]. However, due to the intricacy linked to the orally disintegrating tablet (ODT), only a limited number of medications containing bitter compounds have been successfully brought to market.



Flow Chart for the Development of Oral Solid Dosage Form

Oral fast dissolving film (OFDF) is a new method that enhances consumer acceptability due to its quick

disintegration and ability to be self-administered without the need for water or chewing. The film serves as an optimal drug delivery method that dissolves rapidly in the mouth. It effectively meets the market's unfulfilled requirements, is user-friendly and easy to administer. Additionally, it comes in a simple and handy package, reduces unpleasant taste, and is uncomplicated to make. The film is positioned either on the upper surface or the lower surface of the tongue. The active substance is quickly released for absorption, either locally or systemically, and remains at the place of application. The creation of a rapidly dissolving film presents a chance to expand the product line in the market. Various drugs such as neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic drugs, and drugs for erectile dysfunction can be potential options for this type of medication delivery [7,10-16].

There is a wide range of medications that can be developed into mouth dissolving films. Novel drugs have the potential to expand the range of treatment options in the indicated areas [12,17].

- Pediatrics (Antitussives, Expectorants, Antiasthmatics)
- Geriatrics (Antiepileptic, Expectorants)
- Gastrointestinal diseases
- Nausea (due to Cytostatic therapy)
- Pain (Migraine)
- CNS (Antiparkinsonism therapy)

Salient Features of Fast Dissolving Oral Film

- Ease of administration for patients who are mentally ill-disabled & uncooperative.
- Requires no water; have quick disintegration and dissolution of the dosage form.
- Leaves minimal or no residue in the mouth after administration.
- No risk of choking.
- Provide advantages of liquid medication in the form of solid preparation.
- Amenable and adaptable to existing processing and packaging machinery [9].

Advantages of Fast Dissolving Oral Film

Fast dissolving oral film combines all the advantages of tablets (accurate dose, self-administration) with those of liquid dosage forms (easy swallowing, quick

bioavailability). The administration of drugs by the oral route has several advantages^[9-10,20-24] over other route of administration such as;

Clinical Advantages:

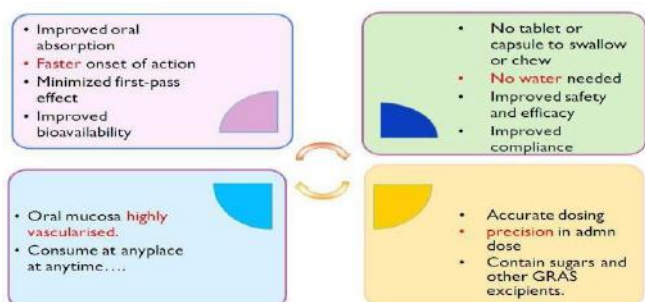
- Improved oral absorption
- Improved bioavailability due to less amount of degradation of drug.

Medical Advantages:

- Overcomes unacceptable taste of drugs by masking bitter taste of drugs with taste masking agents.
- Improved patient compliance, especially patients suffering from dysphasia and pediatric and geriatric population.

Technical Advantages:

- Contain sugars and other GRAS excipients.
- Improved stability due to better packaging.
- No special set up required for the industry.



Advantages of FDOF.

Disadvantages of Fast Dissolving Oral Films

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Taste masking- Most drugs have bitter taste, and need taste masking.
- Special packaging- OFDFs are fragile and must be protected from water so it needs special packaging.
- Dose uniformity is a technical challenge
- Expensive packaging of oral film^[7,10,20].

Special features of Fast Dissolving Oral Films

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion [7,12,24,30]
- Fast disintegration
- Rapid release

Comparison between Oral Films and Oral Disintegrating Tablets.

Larger surface area gives greater dissolution	Less surface area gives less dissolution than ODF
ODF are flexible and durable	ODT are brittle and less durable than ODF
Only Low dose can incorporated in formulation	High dose can incorporated in formulation
ODF thickness are 50 to 500 µm	ODT thickness as like convention tablet
Patient Compliance is more	Patient compliance is less than FDOF ^[31-33]

Comparison of fast dissolving oral film over other dosage forms.



Benefits of Fast Dissolving Oral film over Fast Disintegrating Tablets

- Provide a larger effective surface area for the disintegration.
- No friability loss
- Require less expensive processing and packaging materials
- No fear of choking

- Requires less excipients^[20,32]
- Less time consuming process.
- More elegant
- More economical

Classification of Oral Film

The three types of oral films are differentiated from each other in following table.

Classification of Oral Films ^[33]

Property/sub type	Flash release wafer	Mucoadhesive melt- av	if er
Area (cm ²)	2-8	2-7	
Thickness (mm)	20-70	50-500	
Structure	Single layer	Single or multilayer system	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue(upper palate)	Gingival or buccal Region	Gingival, (Other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes forming gel	Maximum 8-10 hours depending on the specific needs.
Site of action	Systemic or local	Systemic or local	Systemic or local

Formulation development

Criteria for selection of Excipients along with their Concentration.

S.NO	CATEGORY	CONC (%)
1.	Drug	1-25
2.	Polymer	40-50
3.	Plasticizer	25-35
4.	Sweetener	2-10
5.	Flavor	2-5

Choice of drug candidate

Suitable drug candidate for FDOF should posses:

- No bitter taste
- Good stability in water and saliva
- Dose should be low as possible.



Drug Candidates.

2-4

50-250

II. SELECTION OF POLYMERS

Low/non-soluble polymers

Various polymers may be employed in the film production of FDOF, with a maximum composition of 40% w/w. Polymers are the primary contributors to the film's strength. The film should possess durability to mitigate any harm throughout the process of handling and shipping. The polymers may be used individually or in combination, depending on the specific needs. The examples of polymers are as follows: The following substances are included: Hydroxyl propyl methyl cellulose (HPMC), Hydroxy Propyl cellulose, Starch and modified starch, Pullulan, Pectin Gelatine, Carboxyl methyl cellulose, PVP + Cross linked PVP, Alginates Poly vinyl Alcohol, Malt dextrose, and others....

Plasticizer

Plasticisers have a positive function in the preparation of fast dissolving films. Plasticiser enhances the pliability of the film and diminishes its fragility. The plasticiser must exhibit compatibility with both the polymer and solvent. The use of a plasticiser improves the flow characteristics of the polymer and boosts its strength. Propylene glycol (PG), Polythene glycol (PEG), Glycerol, Phthalate derivatives include dimethyl, diethyl, and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin, and castor oil are often used plasticisers. The presence of plasticiser might result in the occurrence of film breaking, splitting, and peeling. Furthermore, it has been noted that the use of certain plasticisers may also impact the pace at which the medicine is absorbed. The Plasticiser should possess a high degree of volatility.

Flavourants

It includes:

1. Both natural and artificial flavour such as artificial vanilla, cinnamon, and various fruit flavours, either individual or mixed.
2. Mints such as peppermint, menthol.
3. Essential oils such as thymol, eucalyptol and methyl salicylate.

Sweeteners

Sweeteners include both natural and artificial sweeteners as:

Natural sweeteners include monosaccharide's, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof;

Water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like and free acid form of saccharin and dipeptide based sweeteners. Aspartame, Neotame are successfully use for the taste masking.

Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the FDF. Generally acids are used as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%.

III. METHOD OF PREPARATION

Different methods for achieving fast dissolving film formulation by the following

1. Casting and drying
 - A. Solvent casting
 - B. Semisolid casting.
2. Freeze dried wafer
3. Extrusion
 - A. Hot melt extrusion.
 - B. Solid Dispersion Extrusion
 - C. Rolling method.

Casting and drying

Solvent casting Method

- Preparation of the casting solution,
- Deaeration of the solution,
- Transfer of the appropriate volume of solution into a mold,
- Drying the casting solution,
- Cutting the final dosage form to contain the desired amount of drug,
- Packaging The Oral fast dissolving films are prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution is continuously stirred up to 4 hours on magnetic stirrer^[9,10,12,26] and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water soluble excipients i.e. sweetening agent, saliva-stimulating agent, flavor and drug are dissolved with constant stirring for 45 min. When the stirring is over both the solutions are mixed together with stirring for another 1 hour on magnetic stirrer. Then keep the solution stationary for 1 hour to let the foams settle down. The resulting formulation is casted on a suitable platform and is dried to form a film. The film is preferably air-dried or dried under oven then the film is carefully removed.

Advantages

- Great uniformity of thickness and great clarity then extrusion.
- A typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% RSD.
- Films have fine gloss and freedom from defects such as die lines.
- Films have more flexibility and better physical properties. The preferred finished film thickness is typically 12-100µm.

Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

Semisolid casting:

In the semisolid preparation water soluble polymer add in it and this preparation add in acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate) which is prepared by the ammonium, sodium hydroxide then finally add sufficient amount of plasticizer form a gel and it casted^[9,12,26]. Acid insoluble polymer with film forming polymer ratio is 1:4 and film thickness is 0.015 to 0.05 inches.

Freeze dried wafer

Is also known as Lyophilisation or Cryodesiccation method in that dehydration of water and reduce pressure from surrounding to allow the water in material to sublime directly from solid phase to gaseous phase. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

Extrusion

Hot melt extrusion

In the hot melt extrusion drug mixed with carrier in the solid form. Extruder having extra facility with heater it melt the solid form carrier and drug then this melt is place in the dies and cut in to specific shape^[9-10,12,26].

E.g. Maltodextrin can be used to produce fast-dissolving films with a high drug loading capacity by hot-melt extrusion technology.

Advantages

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the APT may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages

- Thermal process so drug/ polymer stability problem.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers

Solid Dispersion Extrusion:

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. In this method^[9,10,12,26] drug is dissolved in a suitable liquid solvent then solution is incorporated into the melt of polyethylene glycol, obtainable below 70°C and finally the solid dispersions are shaped into the films by means of dies.

Rolling method:

In this preparation drug containing suspension having water or alcohol as solvent is added on drum then evaporated the solvent^[9,10,12,26] and cut in specified shape.

IV. VARIOUS TECHNOLOGIES USED IN ORAL FILM FORMULATION

XGel:

XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

Soluteaves:

This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. Solute leave technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form.

Wafertab:

Wafertab is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting.

Foam burst:

Foam burst is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure.

The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-the mouth sensation^[9,33].

Micap:

Micap Signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the Bio Progress

water-soluble films.

Patented Technologies:

The patented technologies for manufacturing of fast dissolving drug delivery system are Zydus, Orasolv, Durasolv, Flashdose, Wowtab and Nanocrystal Technology.

EVALUATIONS

Weight Uniformity:

Films can be weighed on analytical balance and average weight can be determined for each film. It is useful to ensure that a film contains proper amount of excipients and drug.

Thickness:

The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

Dryness Test/Tack Tests:

About eight stages of film drying process have been identified and they are set-to touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat dry print free. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study^[7,10,12,22,26].

Tensile Strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{Film width}}$$

pH value:

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH.

Tear resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically, very low rate of loading 51 mm (2 in.)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as

the tear resistance value in Newton's (or pounds-force).

Young's modulus:

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{Crosshead space}}$$

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Folding endurance:

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Disintegration time:

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.

Dissolution test:

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

Assay/drug content and content uniformity:

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia.

Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.

Organoleptic evaluation:

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial

methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high throughput taste screening of oral pharmaceutical formulations.^[34]

List of Marketed Fast Dissolving Oral Films

Table: List of Marketed FDOF

S.No.	Product	Manufactured By
1	Dextromethorphan HBr (cough suppressant), Diphenhydramine Citrate (cough and cold), Breath Strips	MonoSolRx
2	Donepezil rapid dissolving films, Ondansatran rapid dissolving films	Labtec Pharma
3	Life-saving rotavirus vaccine to infants	Johns-Hopkins biomedical engineering students.
4	Methylcobalamin fast dissolving films, Diphenhydramine HCl fast dissolving films, Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films	Hughes-medical corporation
5	Altoid cinnamon strips, Boots vitamin c strips, Cool shock peppermint strips, Benzocaine films, Caffeine films	Dow-chemical company

V. APPLICATIONS OF FAST DISSOLVING ORAL FILMS

Oral films are preferred for local action and also to manage pain, allergies, sleeping difficulty and CNS disorders^[26-28].

Topical applications:

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

Gastro retentive dosage systems:

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or

enzyme secretions of the gastrointestinal tract, and used to treat gastrointestinal disorders.

Diagnostic devices:

Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

Vaccines:

Fast dissolving films can be delivered in the form of vaccine which is stable at room temperature so it is quickly dissolved in mouth and in saliva. Rotavirus vaccine prepared in United States is room temperature stable fast-dissolving buccal film delivery system for vaccines.

- Oral films are applicable to enhance the bioavailability of poorly bioavailable drugs.
- Taste masking of bitter drugs.
- Dissolvable films are loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.

VI. CONCLUSION

Lately Rapidly disintegrating films have become more common as oral dose formulations for breath fresheners. Pharmaceutical firms have acknowledged the possibility of leveraging this technology to develop therapeutic treatments and have introduced many items for the over-the-counter (OTC) market. The literature provides little description and investigation of rapid dissolving thin films. However, these films seem to be an optimal dose form for administration to young children, particularly in geriatric and paediatric patients. They possess the enhanced stability of a solid dose form while also offering the convenient application of a liquid. The limited availability of goods on the market is due to the absence of a standardised process for their manufacture and analysis.

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